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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,311	06/21/2001	Liselotte Bjerre Knudsen	5515.214-US	6961

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NOVO NORDISK PHARMACEUTICALS, INC.
100 COLLEGE ROAD WEST
PRINCETON, NJ 08540

EXAMINER	
MOHAMED, ABDEL A	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,311	KNUDSEN ET AL.	
	Examiner	Art Unit	
	Abdel A. Mohamed	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *92,93,96-99,104-106 and 121-135* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *92,93,96-99,104-106 and 122-135* is/are rejected.

7)☒ Claim(s) *121* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

CONTINUED EXAMINATION UNDER 37 CFR 1.114 AFTER FINAL REJECTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 04/28/06 has been entered.

ACKNOWLEDGMENT OF AMENDMENT, REMARKS AND STATUS OF THE CLAIMS

2. The amendment and remarks filed 04/28/06 are acknowledged, entered and considered. In view of Applicant's request claim 96 has been amended. Claims 92, 93, 96-99, 104-106 and 121-135 are now pending in the application. The rejection under 35 U.S.C. 112, second paragraph is withdrawn in view of Applicant's amendment and remarks filed 04/28/06. However, the objection to the abstract and the rejection under 35 U.S.C. 112, first paragraph are maintained for the reasons of record.

ABSTRACT OF THE INVENTION

3. It is noted that Applicant will present a new abstract if the claims are allowed. However, since the current abstract is not descriptive, a new abstract is required that is

clearly indicative of the invention to which the claims are directed. Thus, the previous objection to the abstract is maintained for the reasons of record.

ARGUMENTS ARE NOT PERSUASIVE

CLAIMS REJECTION-35 U.S.C. § 112 1st PARAGRAPH

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 92-93, 96-99, 104-106, 122, 123-135 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of a pharmaceutical composition containing exendin-3 or exendin-4, fragment thereof, or any combination thereof, for the treatment of diabetes mellitus, does not reasonably provide enablement for an exendin derivative particularly, a derivative of an analogue of exendin-4 wherein said analogue has an amino acid sequence that differs from the amino acid sequence of exendin-4 by the substitution of up to ten (claim 92) or up to six (claims 93 and 124) or up to 4 (claim 127) amino acid residues with any α-amino acid residue or at any C-terminus of exendin-4, wherein (a) one lipophilic substituent is attached to amino acid residues and (b) one of the lipophilic substituent is attached to an amino acid residue which is not the N-terminal or C-terminal amino acid residue (claims 92 and 93), to a pharmaceutical formulation comprising the composition of claim

92 as an active ingredient (for claim 122) or composition of claim 93 (for claim 130) or composition of claim 124 (for claim 132) or composition of claim 127 (for claim 134) and to a method of treating insulin dependent or non-insulin dependent diabetes mellitus by administering a therapeutically effective amount of the composition of claim 92 (for claim 123) or claim 93 (for claim 131) or claim 124 (for claim 133) or claim 127 (for claim 135), respectively. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

Applicant's arguments filed 04/28/06 have been fully considered but they are not persuasive. Applicant has argued that a) the Examiner has alleged that undue experimentation would be required to determine all species of exendin analogs that could be derivatized with a lipophilic substituent as presently claimed; b) the test of enablement is whether one reasonably skilled in the art would make and use the invention from the disclosure in the application coupled with information known in the art without undue experimentation; c) the Examiner erred in ignoring and/or failing to consider and appreciate the evidence provided by Applicant in the amendment filed 12/23/04 because numerous exendin analogs which retain biological activity had been identified as had specific substitutions that could be made at specific residues of exendin-4; d) it was known in the art which residues in exendin-4 could be changed to produce exendin-4 analogs that stimulate insulin release and specific analogs had been described as had methods for identifying further analogs; e) in addition, further evidence that the experimentation necessary to determine those changes can be made in the

exendin-4 sequence is provided by WO 98/05351; and f) Applicant concludes by stating that taken as a whole, it is seen that the supporting disclosure is commensurate in scope with the methods as claimed, and as such, there is insufficient evidence to support the rejection as set forth in the Official Action, that one having ordinary skill in the art could practice the claimed invention without undue experimentation, and that the requirements of the first paragraph of 35 U.S.C.§ 112 have been met is not persuasive.

Contrary to Applicant's arguments, there is no teachings in the specification or evidences provided on 12/23/04 and 04/28/06 (i.e., WO 98/05351) to show the enablement for using up to ten or six or four amino acid residues with any α-amino acid residue or at the C-terminus of exendin-4 suggests that the amino acid sequence/residue intended to be modified by substitution is either is not known or Applicant contemplates modification of an exendin derivative by substitution from 0 to 10 of amino acid residues in the peptide. The evidences provided on 12/23/04 and 04/28/06 have been considered, but, the showing of evidences provided is not commensurate in scope of the claims because half of the structures claimed are intended to changeable and/or substituted. Thus, the scope of the claims is not commensurate with the enablement provided by the disclosure of the instant invention nor the evidences provided therewith with regard to the amino acid residues identified by substitution of up to ten or six or four amino acid residues with any α-amino acid residue or at any C-terminus of exendin-4 for the reasons of record. Further, Applicant has provided little or no guidance beyond the mere presentation of sequence data (i.e., SEQ ID NOS: 1-3) to enable one of ordinary skill in the art to determine without undue

experimentation by substitution of up to ten or up to six or up to four amino acid residues with any α- amino acid residue or any C-terminus of exendin-4 in the manner claimed in claims 92, 93, 124 and 127.

Furthermore, Applicant has provided the sequences of exendin derivatives as disclosed in SEQ ID NOS: 1-3. From this Applicant is attempting to extrapolate to a broad diversity of exendin peptides bearing little relationship to exendin derivatives disclosed in the specification by claiming the substitution of up to ten or six or four amino acid residues with any α-amino acid residue or any C-terminus of exendin-4. Thus, either in claim 92 or 93 or 124 or 127, any number of amino acids (at least from 0 to 10) can be replaced with any number ranging from 1-10 conservative or non-conservative substitution by insertion and/or deletion. The effects of this are unknown for the reasons of record, and as such, when this variable is added, the claimed invention becomes little more than conjecture. Moreover, without guidance, the changes which can be made in the peptide/protein structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessary and improperly, extensive and undue. See *Amgen Inc. V. Chuqai Pharmaceutical Co. Ltd.*, 927 F.2d, 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) At 18 USPQ2d 1026-1027 and *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1986).

Furthermore, with respect to claims 122 and 123 or claims 130 and 131 or claims 132 and 133 or claims 134 and 135, there is no working example or data or evidence which shows the claimed exendin derivative is useful as a pharmaceutical composition containing as an active ingredient a therapeutically effective amount of the exendin

derivative administered to treat diabetes as claimed in claims 122, 123 and 130-135. Although, there is protocol for preparation of pharmaceutical compositions as well as certain dosages as recited on pages 30-32 and 41-42, nevertheless, there is no evidence in the instant specification or the evidence provided on 12/23/04 and 04/28/06 to use or administer the pharmaceutical composition in therapeutically effective amount as claimed, except for the demonstration of assays which show the efficacy of GLP-1 derivatives in their ability to stimulate formulation of cAMP in cell lines expressing the cloned human GLP-1 receptors *in vitro* as recited on page 48 in the instant specification disclosing the range of effective dosages of a pharmaceutical composition to be administered for the intended treatment of diabetes. Further, there is not sufficient data or evidence to substantiate such protocols of using pharmaceutical composition of claims 122, 130, 132 and 134 to be administered in a therapeutically effective amount to treat diabetic patients in the manner claimed in claims 123, 131, 133 and 135, respectively. Hence, the only support for the claimed pharmaceutical composition in the specification is Applicant's supposition of the invention as recited in the protocols. Furthermore, Applicant's claims are directed to a very large number of compounds by using specific therapeutically effective amount of a pharmaceutical composition, and there are no objective factual evidence in the specification showing that treatment has occurred using the specific therapeutically effective amount of a pharmaceutical composition claimed. Thus, one cannot administer specific effective amount of a pharmaceutical composition to treat diabetes in all situations without appropriate testing.

Therefore, the scope of the exendin derivative having an amino acid sequence that differs the amino acid sequences disclosed in the instant specification would involve substitution of the amino acid residues in the exendin-4 peptide with any number of amino acid residues ranging from 1-10 conservative or non-conservative. Hence, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making ad using the invention. Moreover, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since any number of amino acid residues ranging from 1-10 are to be substituted with any amino acids identified as exendin-4 are contemplated and are encompassed as well as wide range of situations. The results desired appear to be highly dependent on all variables, the relationship of which is not clearly disclosed. Thus, without guidance through working example(s), one of ordinary skill in the art would not predict from the sequence data disclosed in the instant specification to substitute any number of amino acid residues with a range of at least 1-10 or 1-6 or 1-4 amino acids and be used as a pharmaceutical formulation by administering a therapeutically effective amount of said pharmaceutical formulation to treat diabetic patients (i.e., insulin dependent or non-insulin dependent) in the manner claimed in the instant invention.

Thus, the Examiner is unable to determine the enablement of the invention as claimed without appropriate working examples. The only support for the claimed invention in the specification is Applicant's supposition of the invention in a form of general discussion and certain protocols and improper incorporation of references.

Secondly, the Examiner has clearly shown in the previous Office Actions (mailed 6/28/04 and 03/28/05) and as discussed above that without guidance through working example(s), one of ordinary skill in the art would not predict from the background discussion and/or information and protocols to employ an exendin derivative particularly, a derivative of an analogue of exendin-4 wherein said analogue has an amino acid sequence that differs from the amino acid sequence of exendin-4 by the substitution of up to ten or up to six or up to 4 amino acid residues with any α-amino acid residue or at any C-terminus of exendin-4, wherein one lipophilic substituent is attached to amino acid residues and one of the lipophilic substituent is attached to an amino acid residue which is not the N-terminal or C-terminal amino acid residue, to a pharmaceutical formulation and to a method of treating insulin dependent or non-insulin dependent diabetes mellitus by administering a therapeutically effective amount of the composition thereof in the manner claimed in the instant application. Thus, the specification and the evidences provided do not enable any person skilled in the art to which it pertains, or which it is most nearly connected, to use the invention commensurate in scope with the claims. In the express absence of one or more examples, evidence and sufficient guidance, the skilled artisan would be faced with undue experimentation for practicing the invention. Thirdly, it is not understood from Applicant's response how the instant invention, which Applicant considers as novel and inventive, be exemplified without working example(s) or data or evidence. The law requires that a disclosure in an application shall inform those skilled in the art how to use Applicant's alleged discovery, not how to find out how to use it for themselves. See

In re Gardner et al., 166 USPQ 138 (CCPA 1970). Therefore, in view of the quantity of experimentation necessary, the lack of adequate guidance or working example(s) or data or evidence, and the breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is again suggested.

OBJECTION TO CLAIM, ALLOWABLE SUBJECT MATTER

5. Claim 121 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

ACTION IS FINAL, FIRST ACTION FOLLOWING REQUEST FOR CONTINUED EXAMINATION UNDER 37 CFR 1.114

6. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, THIS ACTION IS MADE FINAL even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CONCLUSION AND FUTURE CORRESPONDANCE

7. Claims 92, 93, 96-99, 104-106 and 122-135 rejected and claim 121 is objected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (571) 272 0955. The examiner can normally be reached on First Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Tsang Cecilia can be reached on (571) 272 0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Jon Weber
Supervisory Patent Examiner

Mohamed/AAM
June 23, 2006